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## Hyaluronan synthase 2 regulates fibroblast senescence in pulmonary fibrosis.

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### Public Summary:

Dysregulated repair of lung injury often results in lung fibrosis characterized by unremitting deposition of matrix components including glycosaminoglycan hyaluronan (HA). HA is mainly produced by hyaluronan synthases (HAS) in mesenchymal cells. We previously demonstrated that over-expression of HAS2 in mesenchymal cells in mice regulates the invasiveness of fibroblasts and promotes severe lung fibrosis. The mechanisms that control the resolution of lung fibrosis are unknown. We propose that a critical step in resolving fibrosis is the induction of senescence in fibrotic fibroblasts and hyaluronan synthase 2 may regulate this process. We found that fibrotic fibroblasts developed the characteristics of replicative senescence in culture and that HAS2 expression was dramatically down-regulated. Furthermore, down-regulation of HAS2 initiated and regulated fibroblast senescence through a p27-CDK2-SKP2 pathway. Deletion of HAS2 in mouse mesenchymal cells increased the cellular senescence of fibroblasts in bleomycin-induced mouse lung fibrosis in vivo. These data suggest that HAS2 may be a critical regulator of the fate of pulmonary fibrosis and we propose a model where over-expression of HAS2 promotes an invasive phenotype resulting in severe fibrosis and down-regulation of HAS2 promotes resolution. Targeting HAS2 to induce fibroblast senescence could be an attractive approach to resolve tissue fibrosis.

### Scientific Abstract:

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